

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205266Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: June 4, 2015

Reviewer(s): Amariyls Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)

Team Leader: Naomi Redd, Pharm.D, Acting Team leader, DRISK

Division Director: Cynthia LaCivita, Pharm.D, Acting Director, DRISK

Drug Name(s): Sonidegib (Odomzo)

Therapeutic Class: Antineoplastic - small molecule inhibitor of the hedgehog signaling pathway

Dosage and Route: 200 mg hard gelatin capsule, oral

Application Type/Number: NDA 205266

Submission Number: Seq. No. 0000 (1) and 0014 (18)

Applicant/sponsor: Novartis

OSE RCM #: 2014-2006 and 2014-2008

***** This document contains proprietary and confidential information ***
that should not be released to the public.**

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of whether a risk evaluation and mitigation strategy (REMS) is necessary for sonidegib (NDA 205266, received by FDA on September 26, 2014), a new molecular entity.

Novartis proposes that sonidegib be indicated for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy [REDACTED] ^{(b) (4)}. Novartis did not submit a REMS with this application; instead, the sponsor initially submitted a risk management plan which was amended on January 23, 2015.

The proprietary name Odomzo received conditional approval on November 26, 2014. The review classification for this application is standard.

At the time when this review was completed, sonidegib had not received marketing approval by any health authority.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Sonidegib NDA Introduction, Clinical Overview, Summary of Efficacy, Summary of Safety, proposed risk management plan, and a risk management support document ("Justification for Utilizing an Enhanced Pharmacovigilance Program to Assess Pregnancy Exposure and Outcomes) received by FDA on September 26, 2014 and the amendment to the proposed risk management plan and risk management support document received on January 23, 2015.
- Sonidegib mid-cycle review meeting slides February 19, 2015.
- Sonidegib mid-cycle review communication letter March 13, 2015.
- Sonidegib FDA clinical review, dated May 29, 2015.
- Sonidegib draft product label, accessed on June 1, 2015.
- Vismodegib, DRISK review, dated January 9, 2012.

3 REGULATORY HISTORY

The regulatory history of sonidegib, pertinent to this review, is as follows:

- **September 26, 2014:** FDA received NDA 205266. Application included a risk management plan.
- **January 23, 2015:** FDA received an amendment of the risk management plan.
- **February 19, 2015:** Sonidegib mid-cycle review. Safety issues identified at that point did not require a REMS.

Important upcoming dates include the following:

- **June 16, 2015:** Wrap up meeting

- **September 26, 2015:** PDUFA date (planned action goal date: Friday, July 24, 2014)

4 ASSESSMENT OF NEED FOR A REMS

4.1 RATIONALE FOR DRUG DEVELOPMENT¹

The most common cancer in the United States is non-melanoma skin cancer (NMSC). The estimated annual incidence in the United States is 1.5-2 million cases: ~80% are basal cell carcinomas (BCCs) and about ~20% are squamous cell carcinomas (SCCs).² BCC is usually amenable to local treatment. Recurrence rates after initial surgical excision vary from 5-14% but a small proportion may progress to advanced local disease (inoperable) or metastatic disease, which result in significant morbidity (i.e., local tissue invasion and destruction) and mortality. In addition, BCC may metastasize to distant areas (e.g., brain, spinal cord, regional lymph nodes, bone, skin, liver). Metastatic BCC is a rare disease with an incidence ranging from 0.0028% to 0.55%. The 5-year survival rate is approximately 10% and the median survival is 8-14 months. The incidence of mBCC is extremely rare, with frequencies ranging from 0.0028% to 0.55% of all BCC cases.

Ultraviolet light exposure is the most significant cause of BCC and SCC. Ultraviolet light induces DNA damage which can result in cell death or repair of damaged DNA by nucleotide excision repair. In BCC, the genes most commonly damaged by ultraviolet light involve the Hedgehog pathway (Hh). BCC show mutations in Hh genes encoding the tumor-suppressor patched homolog 1 (PTCH1) and smoothed homolog (SMO).²

Almost all BCC have demonstrated mutations in Hh signaling pathways genes encoding the tumor-suppressor patched homolog 1 (PTCH1) and smoothed homolog (SMO) result in aberrant pathway activation and uncontrolled proliferation and survival of basal carcinoma cells.¹

Current treatment of BCC include: (1) surgical removal, (2) photodynamic therapy, (3) imiquimod, (4) 5-fluorouracil, (6) radiotherapy, and (7) chemotherapy. Vismodegib, is a Hh pathway inhibitor approved January 30, 2012 in the US for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. The clinical development program for vismodegib showed objective response rates of 43% for locally advanced BCC and 30% for metastatic BCC; complete response rates of 21 % for locally advanced BCC and 0% for advanced BCC. These data demonstrate there is an unmet medical need for new therapies for the treatment of locally advanced and metastatic BCC. Vismodegib has a boxed warning for embryo-fetal death and severe birth defects. The most common adverse reactions for vismodegib ($\geq 10\%$) were muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia. The

¹ Sonidegib Clinical Overview

² Urba W.J., Curti B.D. (2015). Cancer of the Skin. In Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J (Eds), *Harrison's Principles of Internal Medicine, 19e*. Retrieved May 04, 2015 from <http://accessmedicine.mhmedical.com/content.aspx>.

frequency of grade 3 muscle spasms reported in vismodegib clinical development program was 3.6%.

Sonidegib inhibits the Hh signaling pathway by binding to SMO. Novartis is seeking approval for sonidegib 200 mg/day (hard gelatin oral capsules) for the treatment of adult patients with:

- locally advanced BCC who are not amenable to curative surgery or radiation therapy and

(b) (4)

4.2 CLINICAL DEVELOPMENT PROGRAM³

The clinical development program for sonidegib assessed its efficacy and safety in the treatment of patients with locally advanced or metastatic BCC in the pivotal Phase II trial Study A2201 which included 230 patients (ages 18 years or older, median age at randomization was 67 years old in the 200 mg arm and 65 years old in the 800 mg arm) with advanced BCC randomized to treatment with sonidegib 200 mg/day (n=79) or sonidegib 800 mg/day (n=151). There were 86 females enrolled; 69 (80%) were post-menopausal and 17 (20%) were of child-bearing age. Eleven (13%) out of the 17 women of child-bearing age were considered fertile while six patients of child-bearing age were sterile at study entry.⁴ Female patients of child-bearing potential enrolled in the pivotal trial were required to use two forms of contraception during treatment and for six months after the last dose of sonidegib. Pregnant women were excluded from the clinical trial.

4.2.1 Efficacy⁵

The primary efficacy endpoint was confirmed objective response rate (ORR). The pivotal trial demonstrated, according to blinded central review, an ORR of 58% (95% CI: 44.8, 69.7) for 66 patients with locally advanced BCC receiving 200 mg of sonidegib daily.

(b) (4)

4.2.2 Safety

The overall evaluation of safety is based on data from 293 patients who received ≥ 1 dose of study drug. The analysis includes data from patients in the pivotal trial (Study A2201) and data from adult patients with advanced solid tumors who received treatment with sonidegib at doses of up to 800 mg once-daily.

Adverse drug reactions occurring with an incidence of $\geq 10\%$ in either dose group were muscle spasms, alopecia, dysgeusia, fatigue, nausea, blood creatinine kinase (CK) increased, musculoskeletal pain, weight decreased, diarrhea, decreased appetite, myalgia, abdominal pain, headache, pain, and constipation. The most common grade 3 or 4

³ Sonidegib Clinical Overview.

⁴ Sonidegib FDA clinical review, dated May 29, 2015.

⁵ Clinical Review, Division of Oncology Products 2, dated May 29, 2015.

adverse drug reactions with an incidence of $\geq 2\%$ in the 200-mg treatment group were blood CK increased, lipase increased, fatigue, and muscle spasms.

The incidence of rhabdomyolysis, defined as increased serum CK of more than ten times the baseline values with a concurrent 1.5 fold or greater increase in serum creatinine above baseline values, was 0.2 %. The incidence of muscle toxicity requiring medical intervention (intravenous hydration, magnesium sulfate supplementation, and analgesics or narcotics) was 27%. The risk of musculoskeletal adverse reactions was dose-related over the dose range from 100 mg to 3000 mg sonidegib daily.⁶

Musculoskeletal adverse reactions occurred in 68% (54/79) of patients treated with sonidegib 200 mg daily in the pivotal trial. The most frequent manifestations of musculoskeletal adverse reactions were increase serum CK levels (61%), muscle spasms (54%), musculoskeletal pain (32%), and myalgia (19%). The incidence of severe or life-threatening (Grade 3 or 4) musculoskeletal adverse reactions among patients treated with sonidegib 200 mg daily in the pivotal trial was 9%. Fifteen percent of patients in the pivotal trial who experienced musculoskeletal adverse reactions required temporary interruption or permanent discontinuation of sonidegib and 30% required medical interventions for management of musculoskeletal adverse reactions.

Based on the mechanism of action of sonidegib, there is a significant concern regarding potential teratogenic effects. In animal reproduction studies, sonidegib was embryotoxic, fetotoxic, and teratogenic at maternal exposures below the recommended human dose of 200 mg.

4.2.3 Overall Benefit:Risk Assessment

Advanced BCC is a serious disease which is often disfiguring and potentially life-threatening. There is a medical need for treatment options for patients whose lesions are not amenable to surgery (b) (4).

Based on the available data, the clinical reviewer (Dr. Denise Casey, Division of Oncology Products 2) has recommended full approval of sonidegib at a dose of 200 mg daily for the treatment of patients with locally advanced BCC who are not amenable to curative surgery or radiation therapy. (b) (4)

4.3 RISK MANAGEMENT APPROACH

A REMS was not submitted with this application but the sponsor proposed a voluntary risk management program to manage the risks of myopathy/rhabdomyolysis, teratogenicity and impaired fertility. The objectives of the proposed risk management plan are to educate prescribers about these risks and appropriate prescribing behaviors and to educate patients about the risks. DRISK provided the sponsor the following comments regarding their proposal on November 16, 2014:

Your submission from September 26, 2014 includes a proposal for additional risk mitigating activities (b) (4)

⁶ Sonidegib, draft labeling accessed in SharePoint on June 1, 2015.

addressing the risks of myopathy/rhabdomyolysis and reproductive toxicity and fertility.



FDA advises the Applicant that the additional risk mitigation materials you propose are considered promotional in nature and should be submitted to FDA for review separately with other promotional materials.

The amended risk management plan received by FDA on January 23, 2015 did not include the risk of myopathy/rhabdomyolysis because the sponsor determined that this risk could be managed through labeling only.

There are several FDA approved products associated with myopathy/rhabdomyolysis for which the risk is managed through labeling only (e.g., statins). Of note is the fact that the frequency of serious (grade 3) muscle spasms reported by vismodegib clinical development program was 3.6% versus 9% in the sonidegib clinical program. DRISK recommends managing the risk of drug-induced myopathy/rhabdomyolysis associated with sonidegib through labeling given: (1) the anticipated small prescriber and patient populations and (2) the prescriber population will likely be limited to specialized healthcare providers with expertise in managing and monitoring patients for the serious adverse effects frequently associated with chemotherapy.

The most concerning risk of sonidegib is teratogenicity; this risk is shared with the other drug in class, vismodegib. Past regulatory decisions for communicating the risk teratogenicity associated with vismodegib was through product labeling only (boxed warning, Medication Guide). However, DRISK has a low threshold for re-evaluating the need for a REMS, particularly if the treated patient population expands or if new safety data become available indicating that product labeling alone is not effective at managing the risk of teratogenicity.

In addition to labeling (i.e., boxed warning for embryo-fetal toxicity, patient counseling information and a Medication Guide), FDA requested the sponsor conducts a Pregnancy Pharmacovigilance Study to evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib.

5 CONCLUSION AND RECOMMENDATIONS

The clinical development program for sonidegib demonstrated that this drug is effective in the management of patients with locally advanced BCC. The safety profile of sonidegib includes the risk of teratogenicity which is also associated to vismodegib, the other drug in the class. At this time, DRISK and the Division of Oncology Products 2 determined that a REMS is not necessary to ensure the benefits outweigh the serious risks associated with sonidegib and these risks will be communicated through product labeling (boxed warning, warnings and precautions section, patient counseling information and a

Medication Guide). Please keep DRISK informed if new safety information becomes available that would necessitate this benefit: risk profile to be re-evaluated.

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/s/

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06/04/2015

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